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Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure

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Abstract

Introduction

From a prospective multi-center multi-country clinical trial, we developed and validated risk models to predict prospective all-cause mortality and HF-hospitalizations in patients with heart failure (HF).

Methods

BIOSTAT-CHF is a research program designed to develop and externally validate risk-models to predict all-cause mortality and HF-hospitalizations. The index cohort consisted of 2,516 patients with HF from 69 centres in 11 European countries. The external validation cohort consisted of 1,728 comparable patients from 6 centres in Scotland, UK

Results

Patients from the index cohort had a mean age of 69 years, 27% were female, 83% were in NYHA class II-III and the mean left ventricular ejection fraction was 31%. The full prediction models for mortality, HF-hospitalization and the combined outcome, yielded c-statistic values of 0.73, 0.69, and 0.71 respectively. Predictors of mortality and HF-hospitalization were remarkably different. The 5 strongest predictors of mortality were a greater age, higher BUN and NT-proBNP, lower hemoglobin and failure to prescribe a beta-blocker. The 5 strongest predictors of HF-hospitalization were greater age, previous HF-hospitalization, presence of edema, lower SBP and lower eGFR. Patients from the validation cohort were 74 years, 34% were women, 85% were in NYHA II-III and mean LVEF was 41%; c-statistic values for the full and compact model were comparable to the index cohort.

Conclusion

A small number of variables, which are usually readily available in the routine clinical setting,

provide useful prognostic information for patients with heart failure. Predictors of mortality were remarkably different from predictors of HF-hospitalization.

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Introduction

Accurately predicting risk of mortality or heart failure hospitalization in patients with heart failure (HF) might lead to intensified monitoring and treatment (1–8) and help physicians, nurses and patients in making better management decisions (9). Also, selecting high risk patients in phase III drug and device trials may enrich clinical event rates and decrease sample size.

Many risk prediction models for patients with HF have been published (10). Of 117 models included in a recent meta-analysis, only 33% were validated in a separate cohort. Most of these models performed only moderately (c-statistic values 0.71, 0.63, and 0.68, for mortality, HF-hospitalization or their composite respectively) (10–14). Patient-data in these models were derived predominantly from randomized controlled intervention trials, which enroll highly selected and motivated patients who volunteer for research, or from administrative data-sets, such as medical insurance claims, that often have diagnostic inaccuracies and fail to record key clinical data such as the blood pressure or a measure of renal function.

BIOSTAT-CHF is a large European project, which was specifically designed to develop and validate risk prediction models in patients with HF (15). In the present report we provide the principal findings of this study.

Methods

The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) recommendation was used as a guideline in developing and validating our prediction models (16).

Patient index and validation cohort

Our models were developed using data from the BIOSTAT-CHF cohort (15). In short, BIOSTAT-CHF enrolled an index cohort of 2,516 patients from 69 hospital centers in 11 European countries predominantly during 2010-2014 and a comparable validation cohort of 1,738 patients from 6 centers in Scotland, UK enrolled predominantly during years 2010-2014. Patients were enrolled as in-patients or from outpatient clinics. The median follow-up in each cohort was 21 months with an interquartile range of 15 and 27 months respectively. Patients from the index cohort were aged >18 years with symptoms of new-onset or worsening HF, confirmed either by a left ventricular ejection fraction (LVEF) of ≤40% or B-type Natriuretic Peptide (BNP) and/or (N-terminal pro) B-type natriuretic peptide (NT-proBNP) plasma levels >400 pg/ml or >2,000pg/ml, respectively, treated with either oral or intravenous furosemide ≥40 mg/day or equivalent at the time of inclusion. BIOSTAT-CHF was also designed to establish the effects of and response to initiation and up-titration of and response to guideline directed medical therapy. Therefore, in order to be considered for enrollment in either cohort, patients had either not to be treated with an ACE-inhibitor/ARB and/or beta-blocker or had to be treated with ≤50% of target doses of these therapies at the time of inclusion and with an anticipated initiation or up-titration of such therapy by the treating physician.

Patients from the validation cohort were aged >18 years with a HF diagnosis based on echocardiographic evidence of left ventricular dysfunction or a previous documented admission with HF treated with furosemide ≥20 mg/day or equivalent.

During follow-up, patients underwent a second visit at 9 months after inclusion. Every 6 months, patients were contacted usually by telephone, to collect information on medication and clinical events.

Outcomes and predictor variables

Primary outcomes were time to all-cause mortality, first HF-hospitalization and the composite outcome of all-cause mortality and HF-hospitalization.

Using a Cox proportional hazards model, we evaluated the predictive value of 42 demographic, clinical and biochemical variables that were measured at inclusion. These variables were selected, since previous studies identified those factors to be associated with mortality and hospitalization. An overview of the predictor variables and summary statistics are available in supplemental table (S1).

Non-linearity of the log-hazard for variables with quantitative values were evaluated using restricted cubic splines (17). For the non-linear variables transformations to linearity were applied (e.g. log-transformation or square root) and re-tested using cubic splines. The proportional hazards assumption of the Cox model was assessed using Schoenfeld residuals and the Therneau and Grambsch non-proportionality test (18).

Missing predictor values were imputed using multi-chain Monte Carlo methods with Gibbs sampling. We used the R-package 'mice' (19). We imputed missing data five times, performed the analysis over all five imputations and averaged results using Rubin's rules (19).

Model Development

We conducted stepwise backward regressions on the predictor variables by Akaike information criterion (AIC) in 1000 bootstrap samples for each imputation set (20). We chose variables for our full model when predictor variables were selected in more than 40% of all 5×1000 bootstrap samples. In addition, to make our models more applicable in medical practice, we developed a reduced compact model with a maximum of five predictor variables in the mortality and HF-hospitalization models and ten in the composite model. We used variables selected in the compact model to develop a simplified risk score, using a decision tree algorithm (21), and calculated survival probabilities using Cox regression for all three outcomes.

Model Validation

We first validated our models internally correcting the raw c-statistic (22) for optimism by 1000 bootstrap sampling in the five imputation sets. We used the procedure suggested by Musoro et al (23). Second, we validated our models externally in the validation cohort data. For all patients in this cohort we calculated the risk score using the Cox-regression weights estimated from the index cohort and subsequently calculated the c-statistic for the validation cohort. We then compared the distribution of prediction scores in the index cohort with the distribution of those from the validation cohort. We also applied two prediction models (the Seattle Heart Failure Model (SHFM) (24) and the MAGGIC (25) mortality scores) to the BIOSTAT-CHF cohort

and compared c-statistic values to our developed models. Additionally, we compared c-statistic values in our models for patients with either HFrEF or HFpEF in the index and validation cohorts.

Results

Patients in the index cohort (n=2516) had a mean (±SD) age of 69 (±12) years, 27% were female, 83% were in NYHA II-III with a mean (±SD) LVEF of 31 (±11)%, and 162 (7%) had a LVEF>45%. Further details were previously published, and baseline characteristics of both cohorts are described in supplementary table 1 (15). Most patients were enrolled during an admission for worsening heart failure (55%). During a median follow-up of 21 [15-27] months, 657 (26%) patients died, 613 (24%) were hospitalized at least once for worsening HF and 1,019 (41%) had a first event of either death or HF-hospitalization. Patients in the validation cohort (n=1738) had a mean (±SD) age of 74 (±11) years, 34% were female. 85% were in NYHA II-III with a mean (±SD) LVEF of 41(±13)%, and 529 (34%) had a LVEF>45% (15). Most patients in this cohort were enrolled as out-patients (46%). During a median follow-up of 21 [11-32] months, 589 (34%) patients died and 610 (35%) were hospitalized for worsening of HF, and 894 (51%) had a first event of either death or HF-hospitalization.

Model Development index cohort

Full models

The proportional hazards assumption for the linear effect of the variables on mortality-, HF-hospitalization--risk and the risk of the composite outcome was applicable to all variables. The

final full models included those variables that appeared in >40% of the bootstrap analyses (supplementary figure S1), which for mortality consisted of 16 variables (Table 1) and yielded a raw c-statistic of 0.73 (0.73 after correction for optimism). The relation of each variable with the outcome variables are presented in supplementary table S2. The final full model to predict HF-hospitalization incorporated 10 variables, which achieved a raw c-statistic of 0.69 (0.68 after correction for optimism). The final full model to predict the composite outcome consisted of 15 variables, which had a raw c-statistic of 0.71 (0.70 corrected for optimism).

Compact models

The final compact mortality model included 5 variables that appeared in more than 70% of the bootstrap analyses. Greater age, higher blood urea nitrogen (BUN) and NT-proBNP, lower hemoglobin and failure to prescribe a beta-blocker predicted a higher mortality with a raw c-statistic of 0.69 (0.69 after correction for optimism). The final compact model to predict HF-hospitalization included 5 variables that appeared in more than 60% of the bootstrap analyses. Greater age, HF-hospitalization in year prior to inclusion, presence of edema, lower systolic blood pressure (SBP) and lower estimated glomerular filtration rate (eGFR) predicted an increased risk of HF hospitalization with a raw c-statistic of 0.67, and 0.66 after correcting for optimism. The final compact model to predict the combined endpoint included 9 variables that appeared in more than 70% of the bootstrap analyses. Greater age, HF-hospitalization in the year prior to inclusion, presence of edema, higher NT-proBNP, lower SBP, hemoglobin, HDL-cholesterol, and serum sodium concentration and failure to prescribe a beta-blocker predicted the composite outcome with a raw and optimism corrected c-statistic value of 0.69.

Point score model

For the risk score we used the variables from the compact model. The decision tree algorithm selected the following cut-off points for optimal classification: NT-proBNP >4000 pg/ml, BUN >11 mmol/l, HDL <1.05 mmol/l, age >70 years, sodium <140 mmol/l, hemoglobin (HB) <12 g/dL, eGFR (CKD-EPI formula) <40 ml/min and SBP <140 bpm.

A score for each patient was subsequently calculated by adding one point for each 'adversely' affected variable, resulting in a score range of 0-5, 0-5, 0-9 for mortality, hospitalization, and the combined endpoint respectively. Kaplan Meier survival curves for each score were then calculated (figure 1). The risk scores can be calculated using the online calculator which can be found at: http://www.biostat-chf.eu

In the validation cohort, the c-statistic for the full models were 0.73, 0.64, and 0.68 for mortality, HF-hospitalization and their composite, respectively and 0.72, 0.61, and 0.67 for the compact models. The two-year event rates for risk scores were almost uniformly higher in the validation cohort (figure 1). Calibration plots are presented in supplementary figures S2 and S3. Applying the SHFM and MAGGIC mortality scores to our cohort achieved a similar c-statistic (0.68) to the BIOSTAT compact model.

Difference between HFrEF and HFpEF

In the index cohort, for mortality, HF-hospitalization, and their composite, the final full models yielded c-statistics of 0.73, 0.69, and 0.71 for HFrEF and 0.65, 0.61 and 0.62 for HFpEF and for the compact models 0.69, 0.67, and 0.70 for HFrEF and 0.64, 0.62 and 0.61 for HFpEF. These differences between HFrEF and HFpEF patients in the index cohort were not present in the validation cohort, as presented in table 4. The final full mortality, HF-hospitalization, and their composite models yielded c-statistic values 0f 0.74, 0.63, and 0.68 for HFrEF and 0.72, 0.64 and

0.69 for HFpEF and for the compact models 0.72, 0.62, and 0.67 for HFrEF and 0.71, 0.61 and 0.67 for HFpEF.

Discussion

This analysis demonstrates that a small number of readily available clinical variables predict outcome consistently and with reasonable accuracy in two patient populations with symptomatic HF. Predictors of mortality were remarkably different from predictors of HF-hospitalization.

We recently published a meta-analysis on all available risk-prediction models in patients with HF (10). In 117 models, 249 different variables were used. The mean c-statistic across all models was 0.71, 0.63 and 0.68 for predicting mortality, HF-hospitalization, or their composite, respectively. The BIOSTAT-CHF prediction model for mortality therefore performed slightly better than average. This is remarkable, since BIOSTAT-CHF included much broader and more heterogeneous populations, closer to routine clinical practice, than the populations providing the data for most other HF risk prediction models (10–12).

We provided outcomes of both a full models that included variables that appeared in more than 60% of the bootstrap analyses and compact models that included variables that appeared in more than 70% of the bootstrap analyses. The advantage for the full model are a better predictive value. Given the high number of events, the number of variables that are used in the full model was statistically allowed. The advantage of the full model is that it does justice to the complexity of the large number of factors that determine prognosis of patients. The advantage of the compact model is that it is easier to use, but its limitations should be taken into account.

We also compared our risk scores to two other more complex models based mainly on clinical trial populations; the Seattle Heart Failure Model (SHFM) (24) and the MAGGIC (25) which

reported c-statistics of 0.72 and 0.74 respectively for predicting mortality (24,26). C-statistic values of the SHFM and MAGGIC mortality scores to our cohort achieved a similar c-statistic (0.68) to the BIOSTAT compact model. This supports the hypothesis that our patient population is more heterogeneous, making it more difficult to achieve accurate predictions.

The majority of currently existing prognostic models in patients with heart failure are based on data from randomized controlled trials or extracted from administrative data-sets, such as medical insurance claims. Patients selected for clinical trials are generally a highly selected group of volunteers that have few serious co-morbidities and a high disease burden. Administrative datasets often do not include the detailed medical data needed to develop accurate prediction models. BIOSTAT-CHF included a broad cohort of patients in Europe, with a very limited number of in- and exclusion criteria. And therefore more accurately reflects patients with HF in daily clinical practice.

Similar to many other risk prediction models, we found that the accuracy to predict mortality was moderate, but the model was less accurate at predicting HF-hospitalization. This might be because worsening evidence of HF is not the sole or even dominant factor precipitating hospitalization. Co-morbidity, frailty, community heart failure services, ability to manage life-style and medications, social support networks and cultural factors poorly related to disease severity may all be important determinants of hospitalization (27). Accordingly, no relation has been found between early readmissions and mortality after a first hospitalization (28–31)

The variables that were included in the mortality models were different from those of the HF-hospitalization . The only variable included in all compact models was age. The majority of our

predictors of HF-hospitalization have been described in other models as well. In particular, a previous HF-hospitalization identifies patients at greater risk of (re)hospitalization; it was associated with a more than doubled risk of repeat HF-hospitalization (32). This variable therefore might identify an especially vulnerable patient-group in which fluid balance is easily disrupted, hence causing signs and symptoms of congestion warranting admission and intravenous diuretic treatment. The finding that edema is also a marker of increased hospitalization risk but not of mortality supports this notion and suggests that the underlying pathology might differ significantly (33).

In our mortality model, BUN was an independent predictor, while eGFR was a predictor of re-hospitalizations. BUN is one of the strongest predictors of adverse outcome in HF, and the information captured by this marker is often thought to encompass more than renal function alone (34,35). However, eGFR and BUN are strongly correlated and this in part explains the absence of BUN in the hospitalization model and the absence of eGFR in the mortality model.

Interestingly, serum sodium and HDL are only included in the compact models for the combined endpoint. The inclusion of HDL in these models was not expected beforehand, yet in one report on a small population of patients with advanced HF, HDL was the strongest predictor of an adverse outcome (36). Traditionally, HDL has been associated with the risk of atherosclerosis, however recent evidence showed that the HDL proteome also plays an important role in inflammation (37). Hyponatremia is a well-recognized predictor of poor outcome in both acute and chronic HF and it is therefore not surprising that low serum sodium is associated with an increased risk of the combined endpoint (38,39). The use of a beta-blocker at baseline was associated with a lower risk of mortality and the combined endpoint.

The inclusion of beta-blocker use in our model might be confounded by disease severity influencing tolerability of beta-blockers creating a potential selection bias. In addition, suboptimal medical treatment was an inclusion criterion for our study. However, it may also confirm the importance of the use of beta-blockers in HF and its effect on improved outcome. Further analyses of the BIOSTAT-CHF study will attempt to determine the determinants and clinical outcome related to inadequate up-titration of ACE-inhibitors and/or beta-blockers.

Limitations and Strengths

The BIOSTAT-CHF cohort is a European multi-national prospective cohort. Healthcare systems and patient treatment between the different European countries vary greatly. This might influence management, outcome and prediction, although all investigators were encouraged to follow the recommendations of the ESC HF Guidelines (2). However, because of the multi-national character of this cohort, the results will be highly generalizable. Our validation cohort consisted only of patients from Scotland. This cohort might not resemble the heterogeneity of the European patient population. However, this cohort was a completely independent validation cohort with no ties to the index cohort. Both cohorts selected patients who were sub- optimally treated with ACE-inhibitors/ARBs and/or beta-blockers, which might further limit the generalizability of the results.

Events were not adjudicated by an adjudication committee, but by the treating physicians. However, a systematic meta-analysis failed to detect any effect of event adjudication on study conclusions of cardiovascular outcome trials and the numbers of events included in the final analyses were minimally changed (40).

With regards to the hospitalization endpoint, competing risks need to be taken into account

(i.e. if a patient died, he/she cannot be hospitalized anymore). Both in the index and validation cohorts, BIOSTAT-CHF included patients with HFrEF and HFpEF. This can be regarded as both a strength and a limitation. The HFpEF patients in the index cohort were limited to those patients with NT-proBNP levels >2000 pg/mL, thereby increasing the reliability of the diagnosis but reducing its prevalence and excluding milder cases. There were small differences in c-statistic values between HFrEF and HFpEF in the index cohort, but in the validation cohort, the prediction model performed similarly in patients with either HFpEF or HFrEF. However, given the low number of HFpEF patients in the index cohorts, these data should be carefully interpreted. Finally, the large majority of patients (99%) was Caucasian which limits the generalizability of the models.

Conclusion

We developed and validated models for predicting mortality, HF-hospitalization and the combined outcome of mortality and HF-hospitalization. Variables that were included in the mortality models were remarkably different from those in the HF-hospitalization models. In addition, we presented a simplified risk score for use in clinical practice. In comparison with well-known existing prediction scores, our developed models performed better in this patient population.

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Table 1: Results of the Cox Proportional Hazards analysis for the full models predicting mortality, HF-hospitalization and the combined endpoint.

	Mortality			HF-Hospitalization			Combined endpoint		
	HR	95% CI	p	HR	95% CI	P	HR	95% CI	p
Age (years)	1.03	(1.02-1.04)	<0.0001	1.01	(1.00-1.02)	0.0005	1.02	(1.01-1.03)	<0.0001
Ischemic etiology	1.36	(1.16-1.61)	0.0002						
Heart failure hospitalization in last year				1.68	(1.43-1.98)	<0.0001	1.46	(1.28-1.67)	<0.0001
Smoking									
No								-	-
Past							1.12	(0.97-1.28)	0.1267
Current							1.42	(1.15-1.75)	0.0012
DM				1.32	(1.12-1.57)	0.0009			
COPD	1.28	(1.07-1.54)	0.0084				1.17	(1.01-1.37)	0.0374
NYHA class									
NYHA class I								-	-
NYHA class II							1.17	(0.66-2.08)	0.5822
NYHA class III							1.46	(0.83-2.57)	0.1813
NYHA class IV							1.42	(0.79-2.56)	0.2441
Peripheral edema	1.32	(1.11-1.58)	0.0021	1.28	(1.07-1.53)	0.0052	1.25	(1.08-1.44)	0.002
Elevated Jugular venous pressure									
No		-	-		-	-		-	-
Yes	1.25	(1.00-1.55)	0.0482	1.34	(1.10-1.62)	0.0029	1.22	(1.05-1.42)	0.0084
Uncertain	1.14	(0.80-1.62)	0.4498	1.31	(0.89-1.93)	0.1725	1.16	(0.83-1.63)	0.3984
DBP (mmHg)	0.99	(0.98-1.00)	0.0037						
SBP (mmHg)	1.00	(0.99-1.01)	0.2962	0.99	(0.99-0.99)	<0.0001	0.99	(0.99-0.99)	0.0003
eGFR (CKD-EPI formula)(ml/min)				0.99	(0.99-0.99)	<0.0001	0.99	(0.99-0.99)	0.0064
Log-BUN (mmol/L)	1.39	(1.23-1.58)	<0.0001				1.16	(1.02-1.32)	0.0233
Log-NT-proBNP (ng/L)	1.30	(1.18-1.42)	<0.0001	1.12	(1.02-1.23)	0.0205	1.14	(1.05-1.23)	0.0009
Hemoglobin (g/dL)	0.79	(0.68-0.92)	0.0034				0.91	(0.88-0.95)	<0.0001
Hematocrit (g/dL)	1.05	(1.00-1.11)	0.0626						
Sodium (mmol/L)	0.97	(0.95-0.99)	0.0099				0.98	(0.96-1.00)	0.0026
Log-Total Bilirubin (μmol/L)	1.08	(0.92-1,28)	0.3589				1.11	(0.99-1.24)	0.0798
Log-Alkaline Phosphatase (μg/L)	1.38	(1.14-1.67)	0.0011				1.28	(1.09-1.51)	0.0035

HDL (mmol/L)	0.68	(0.51-0.90)	0.0075	0.69	(0.54-0.88)	0.0031	0.72	(0.57-0.90)	0.0042
Use of beta-blocking agent at baseline	0.75	(0.63-0.89)	0.0009	0.74	(0.62-0.88)	0.0007	0.76	(0.67-0.88)	0.0064

Abbreviations: BUN: blood urea nitrogen; COPD: Chronic Obstructive Pulmonary Disease; DBP: Diastolic Blood Pressure; CI: Confidence Interval; *DM: Diabetes Mellitus; eGFR: estimated Glomerular Filtration Rate; HDL: high density lipoprotein; HF: heart failure; HR: hazard ratio; NT-proBNP: N terminal pro Brain Natriuretic Peptide; SBP: Systolic Blood Pressure*

Table 2: Results of the Cox Proportional Hazards analysis for the compact models predicting mortality, HF-hospitalization and the combined endpoint.

	Mortality			HF-Hospitalization			Combined endpoint		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age (years)	1.02	(1.01-1.03)	<0.0001	1.01	(1.00-1.02)	0.0039	1.03	(1.02-1.04)	<0.0001
Heart failure hospitalization in last year				1.73	(1.47-2.04)	<0.0001	1.52	(1.33-1.74)	<0.0001
Peripheral edema				1.54	(1.31-1.81)	<0.0001	1.40	(1.23-1.61)	<0.0001
SBP (mmHg)				0.99	(0.99-0.99)	<0.0001	0.99	(0.99-0.99)	<0.0001
eGFR (CKD-EPI formula)(ml/min)				0.99	(0.99-0.99)	<0.0001			
Log-BUN (mmol/L)	1.52	(1.35-1.72)	<0.0001						
Log-NT-proBNP (ng/L)	1.40	(1.29-1.53)	<0.0001				1.23	(1.15-1.33)	<0.0001
Hemoglobin (g/dL)	0.89	(0.85-0.93)	<0.0001				0.90	(0.87-0.94)	<0.0001
HDL (mmol/L)							0.61	(0.48-0.78)	<0.0001
Sodium (mmol/L)							0.97	(0.96-0.99)	0.0002
Use of beta-blocking agent at baseline	0.76	(0.64-0.90)	0.0019				0.75	(0.65-0.86)	<0.0001

Abbreviations: BUN: blood urea nitrogen; CI: Confidence Interval; eGFR: estimated Glomerular Filtration Rate; HDL: high density lipoprotein; HF: Heart Failure; HR: Hazard Ratio; NT-proBNP: N terminal pro Brain Natriuretic Peptide

Table 3: C-statistic values of full and compact models for mortality, hospitalization and the combined endpoint.

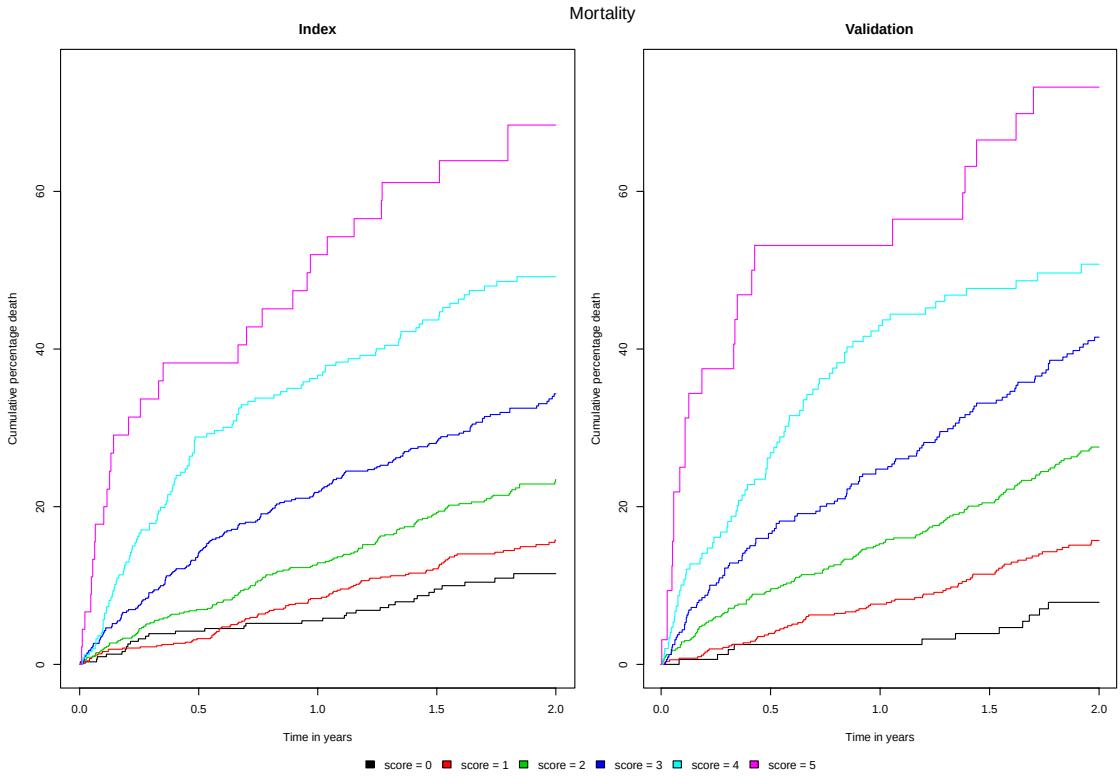
	Model development		Model validation			
	Index cohort		Internal (optimism corrected)		External	
	Full	Compact	Full	Compact	Full	Compact
Mortality	0.73	0.69	0.73	0.69	0.73	0.73
HF- Hospitalization	0.69	0.67	0.68	0.66	0.63	0.63
Combined endpoint	0.71	0.69	0.70	0.69	0.68	0.68

Table 4: C-statistic values of all models for mortality, hospitalization and the combined endpoint in HFrEF and HFpEF patients

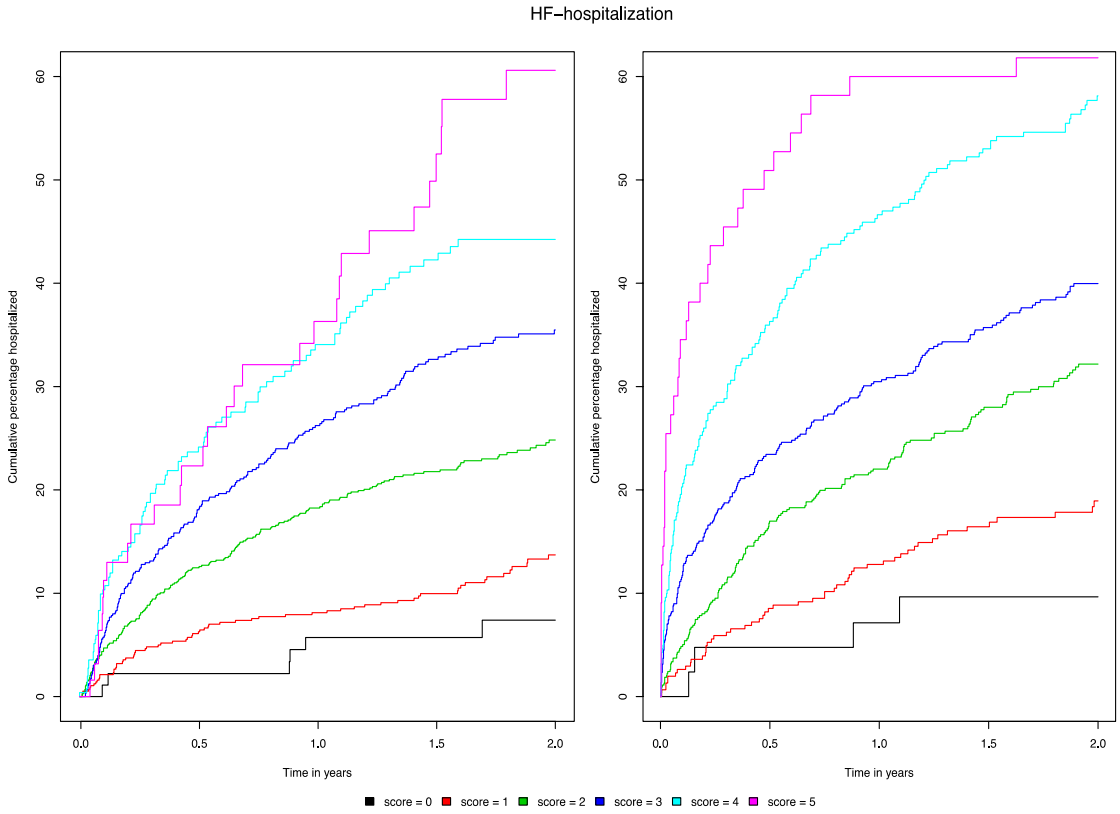
	Index cohort				Validation cohort			
	Full		compact		Full		compact	
	HFrEF	HFpEF	HFrEF	HFpEF	HFrEF	HFpEF	HFrEF	HFpEF
Mortality	0.73	0.65	0.69	0.64	0.74	0.72	0.72	0.71
HF- Hospitalization	0.69	0.61	0.67	0.62	0.63	0.64	0.62	0.61
Combined endpoint	0.71	0.62	0.70	0.61	0.68	0.69	0.67	0.67

Figure 1: Kaplan Meier survival curves for the point scale models (A: Mortality, B:HF-hospitalization, c: Combined endpoint)

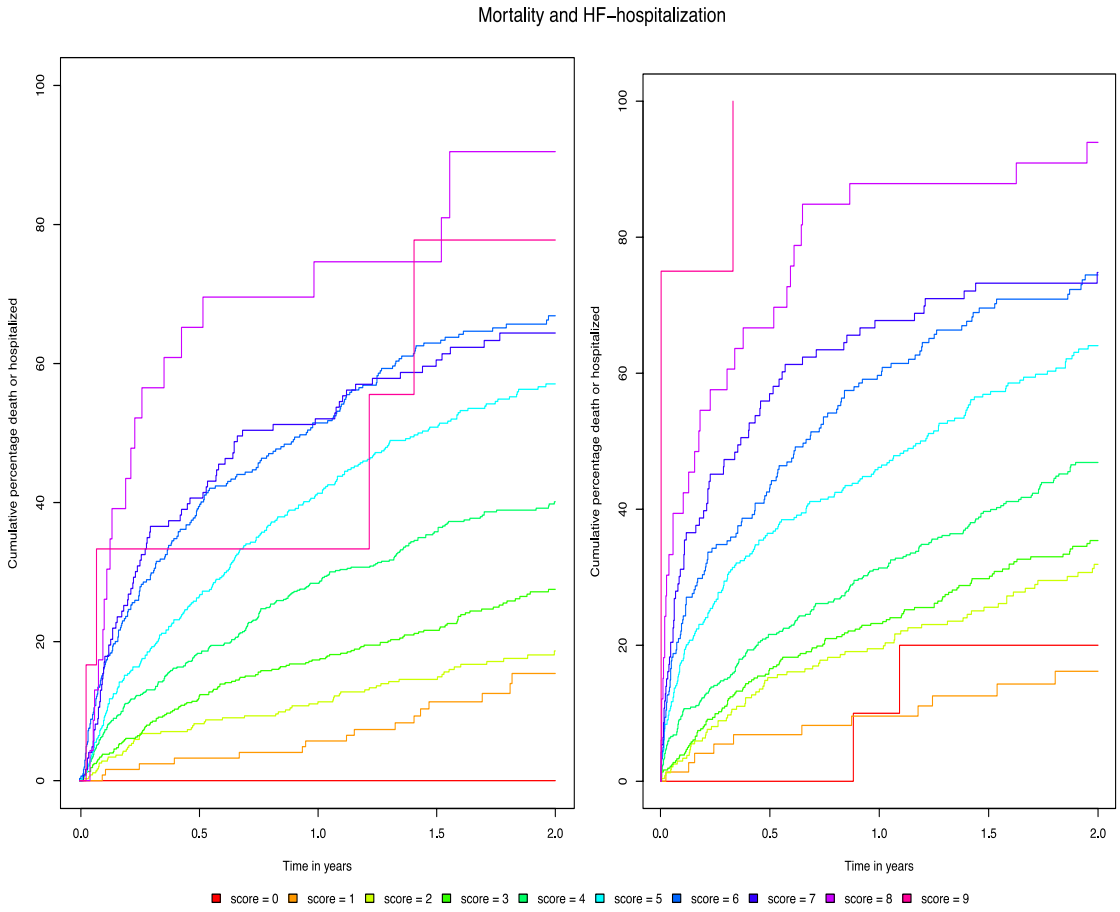
A



B


HF−hospitalization
Cumulative percentage hospitalized
0
10
20
30
40
50
60
0.0
0.5
1.0
1.5
2.0
Time in years
score = 0
score = 1
score = 2
score = 3
score = 4
score = 5

C


Mortality and HF–hospitalization
Cumulative percentage death or hospitalized
0
20
40
60
80
100
0.0
0.5
1.0
1.5
2.0
Time in years
score = 0
score = 1
score = 2
score = 3
score = 4
score = 5
score = 6
score = 7
score = 8
score = 9

Supplementary data

Table S1: Description of each variable used in model development (% (number), mean (sd) or median (interquartile range), with the % and number of values missing for patients

	Index	missing	Validation	missing
Sex (% Male(n))	73.4 (1846)	0% (0)	65.9 (1145)	0% (0)
Age (years)	68.9 (±12)	0% (0)	73.7 (±10.7)	0% (0)
Smoking		0% (0)		1% (12)
Past	48 (*1220*)		35 (602)	
Current	14 (353)		13.7 (236)	
Alcohol usage	28 (700)	1% (4)	47 (790)	2% (40)
Body mass index (kg/m2)	27.9 (±5.5)	2% (38)	28.1 (±6.4)	2% (35)
Heart rate (bmp)	80 (±19.5)	1% (6)	74.2 (±16.6)	2% (38)
Systolic blood pressure (mmHg)	124.7 (±21.9)	1% (5)	125.9 (±22.6)	2% (28)
Diastolic blood pressure (mmHg)	74.9 (±13.4)	1% (5)	69.2 (±13.2)	2% (28)
Left ventricular ejection fraction (%)	31 (±10.6)	11% (273)	41 (±13.0)	9% (163)
HFpEF (LVEF>45%) (%)	7 (162)	11% (273)	34 (529)	9% (163)
NYHA class		3% (70)		1% (1)
I	2.2 (56)		1.0 (17)	
II	34.5 (868)		41.0 (712)	
III	48.8 (1228)		44.4 (772)	
IV	11.7 (294)		13.6 (236)	
Ischemic heart disease (%(n))	60.5 (1358)	11% (273)	64.9 (1128)	0% (0)
Hospitalization in past year before baseline (%(n))	31.6 (794)	0% (0)	26.5 (460)	0% (0)
History of atrial fibrillation (%(n))	45.4 (1143)	0% (0)	43.7 (760)	1% (14)
Diabetes mellitus	32.6 (819)	0% (0)	32.3 (561)	1% (9)
Hypertension (%(n))	62.4 (1569)	0% (0)	57.9 (1007)	1% (7)

eGFR (CKD-EPI formula)(ml/min)	64.4 (47.5-83.4)	6% (155)	66.1 (47.5-83.4)	1% (6)
Myocardial infarction (%(n))	38.3 (963)	0% (0)	48.8 (849)	1% (4)
Coronary Artery Bypass Graft (%(n))	17.2 (433)	0% (0)	17.7 (308)	1% (2)
Percutaneous coronary intervention (%(n))	21.6 (544)	0% (0)	18.7 (325)	1% (18)
Stroke (%(n))	9.3 (233)	0% (0)	18.1 (315)	1% (16)
Peripheral artery disease (%(n))	10.9 (273)	0% (0)	21.5 (374)	3% (45)
Chronic Obstructive Pulmonary Disease (%(n))	17.3 (436)	0% (0)	18.4 (319)	1% (15)
Pulmonary congestion		3% (71)		5% (84)
Single base	12.7 (311)		5.7 (95)	
Bi-basilar	40.1 (980)		38.7 (639)	
Edema (%(n))	29.7 (624)	17% (417)	54.9 (955)	11% (192)
Elevated Jugular venous pressure (%(n))	22 (554)	34% (861)	25.9 (450)	0% (0)
Hepatomegaly (%(n))	14.3 (358)	1% (7)	3.5 (60)	10% (171)
Rales >1/3 up lung fields (%(n))	19.2 (248)	49% (1225)	2.9 (50)	0% (0)
Baseline medication				
Agents acting on the renin-angiotensin system (%(n))	72.3 (1820)	0% (0)	70.1 (1218)	0% (0)
Beta-blocking agents (%(n))	83.2 (2093)	0% (0)	72.7 (1264)	0% (0)
Hematocrit (%)	40.1 (36.3-43.7)	11% (274)	40.5 (37.0-44.3)	1% (18)
BUN (mmol/l)	11.1 (7.4-17.6)	12% (301)	8.6 (6.5-11.9)	1% (9)
NT-proBNP (pg/ml)	4275 (2360-8485.5)	53% (1334)	1376 (510-3548)	2% (29)
Sodium (mmol/l)	140 (137-142)	8% (189)	139.0 (137.0-141.0)	1% (7)
Potassium (mmol/l)	4.2 (3.9-4.6)	8% (192)	4.3 (4.0-4.6)	1% (13)
Bilirubin (μmol/l)	14 (10-21)	45% (1135)	10 (7-15)	1% (20)
HDL cholesterol (mmol/l)	1 (0.8-1.3)	54% (1350)	1 (0.9-1.4)	4% (72)
Alkaline Phosphatase (μg/L)	84 (65-117)	6% (156)	89 (72-116)	1% (10)
Hemoglobin (g/dL)	13.3 (11.9-14.5)	9% (223)	13.2 (11.8-14.5)	1% (16)
Albumine (g/L)	33 (27-38)	6% (156)	38 (34-42)	1% (13)
Alanine aminotransferase (U/L)	25 (19-35)	39% (981)	22 (17-33)	1% (23)
Aspartate aminotransferase (U/L)	25 (17-38)	28% (712)	23 (18-31)	6% (105)
Glucose (mmol/L)	6.3 (5.5-7.9)	25% (622)	6.3 (5.2-8.4)	14% (248)

Abbreviations: BUN: blood urea nitrogen; eGFR: estimate Glomerular

Filtration Rate; HDL: High Density Lipoprotein; HFpEF: Heart failure with preserved ejection fraction, NYHA: New York Heart Association class; NT-proBNP: N terminal pro Brain Natriuretic Peptide

Figure S1: Percentage of bootstrap samples each variables selected. Red and green line are the 40% full and compact model bootstrap sample variable selection lines.

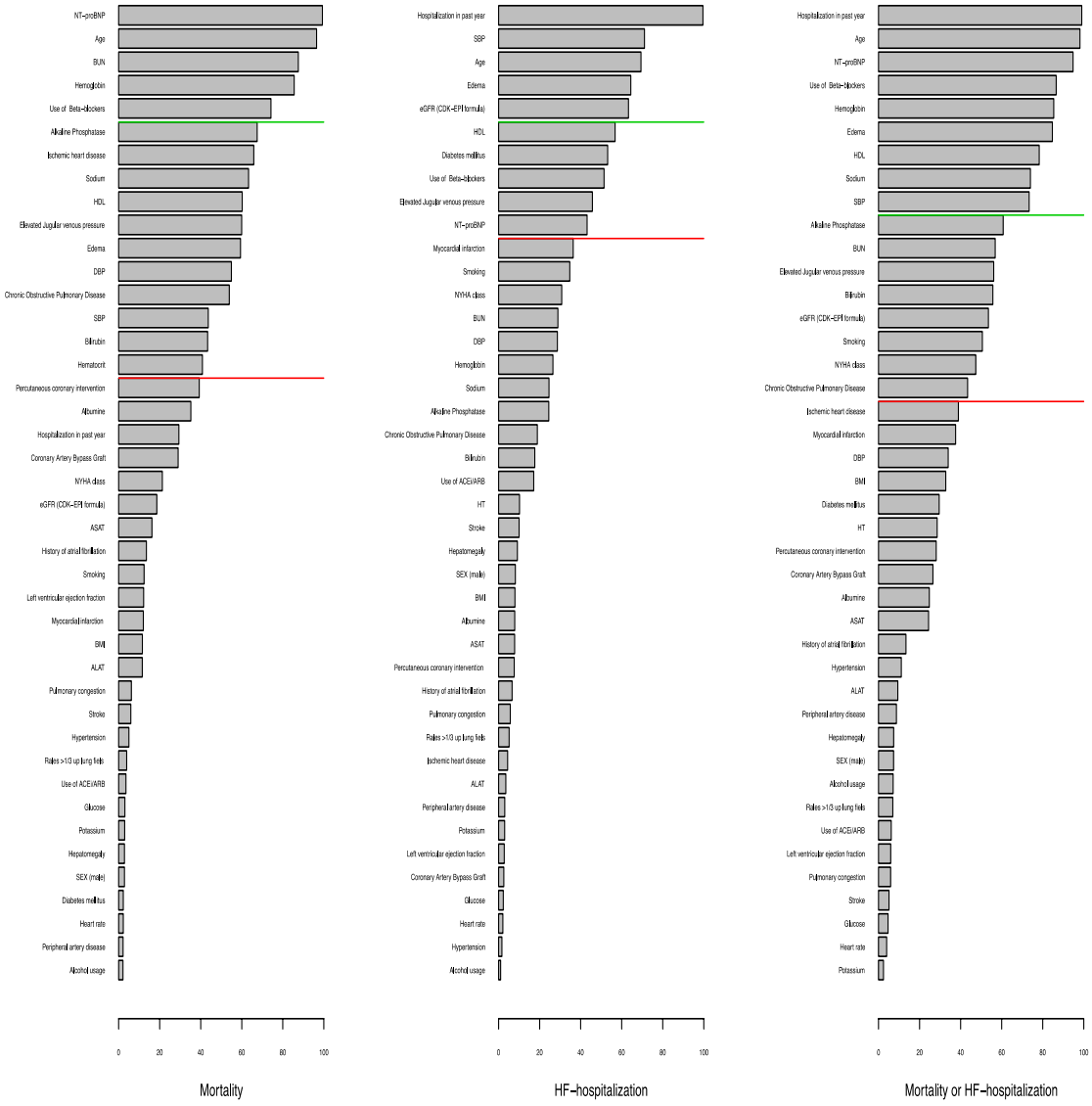


Figure S2: Calibration plot of the compact model in the Index cohort. Gray is the optimal calibrationl, black are the uncorrected calibration lines and blue are the optimism corrected calibration lines

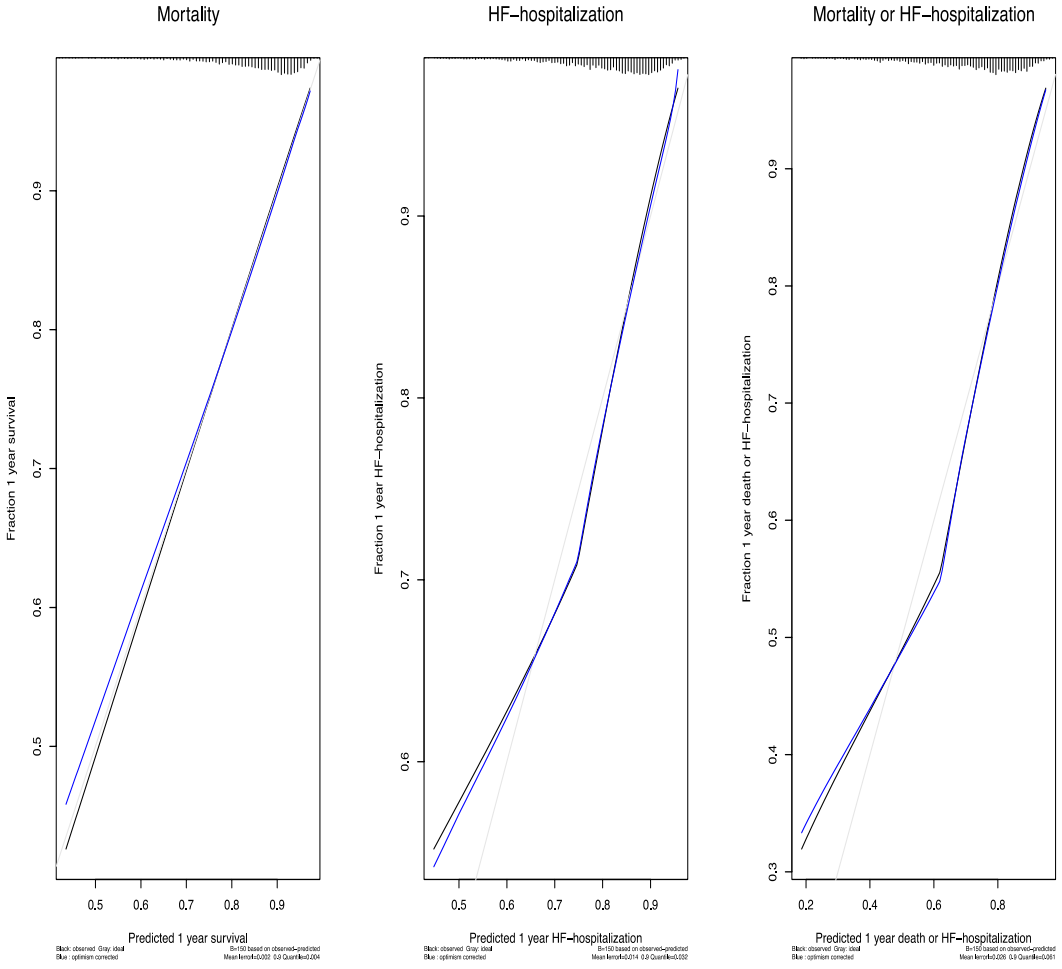


Figure S3: Calibration plot of the compact model in the validation cohort.

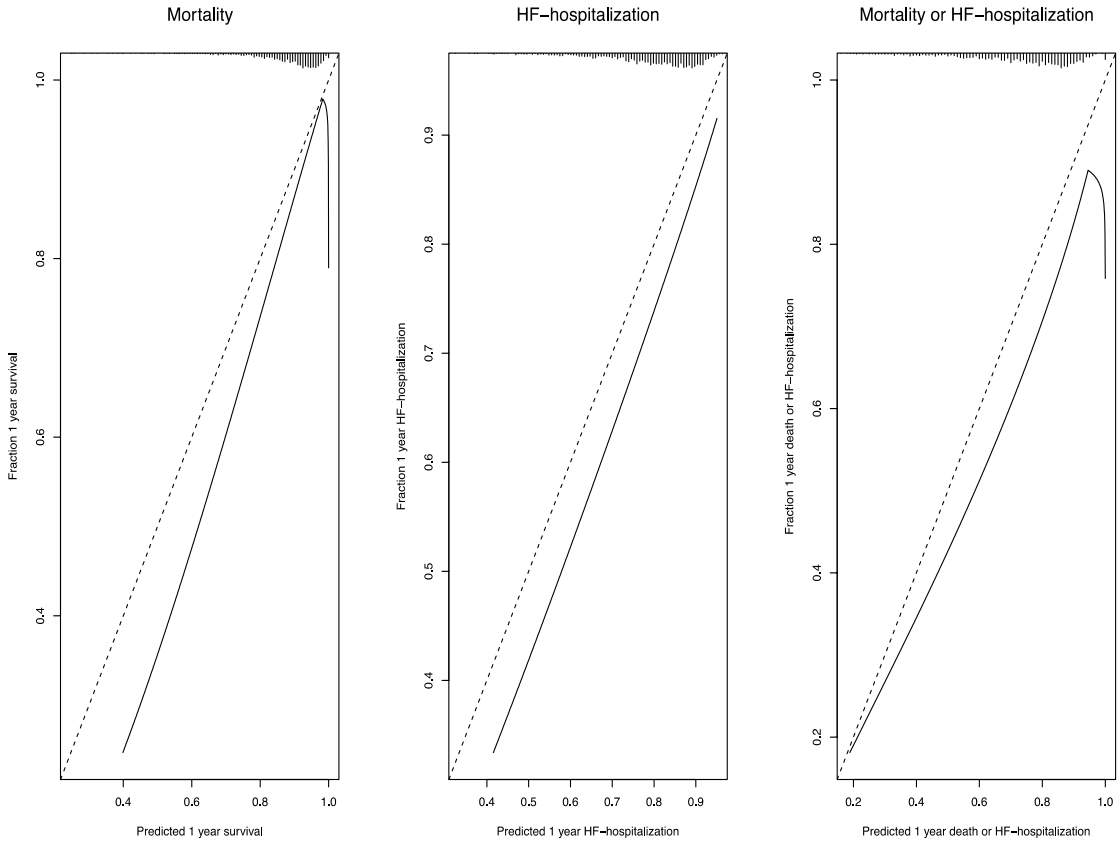


Table S2: Univariate analysis

	Mortality			HF-Hospitalization			Combined endpoint		
	HR	95% CI	p	HR	95% CI	P	HR	95% CI	p
Age (years)	1.03	(1.02-1.04)	<0.0001	1.01	(1.00-1.02)	0.0005	1.02	(1.01-1.03)	<0.0001
Ischemic etiology	1.36	(1.16-1.61)	0.0002						
Heart failure hospitalization in last year				1.68	(1.43-1.98)	<0.0001	1.46	(1.28-1.67)	<0.0001
Smoking									
No								-	-
Past							1.12	(0.97-1.28)	0.1267
Current							1.42	(1.15-1.75)	0.0012
DM				1.32	(1.12-1.57)	0.0009			
COPD	1.28	(1.07-1.54)	0.0084	1.00			1.17	(1.01-1.37)	0.0374
NYHA class									
NYHA class I								-	-
NYHA class II							1.17	(0.66-2.08)	0.5822
NYHA class III							1.46	(0.83-2.57)	0.1813
NYHA class IV							1.42	(0.79-2.56)	0.2441
Peripheral edema	1.32	(1.11-1.58)	0.0021	1.28	(1.07-1.53)	0.0052	1.25	(1.08-1.44)	0.002
Elevated Jugular venous pressure									
No		-	-		-	-		-	-
Yes	1.25	(1.00-1.55)	0.0482	1.34	(1.10-1.62)	0.0029	1.22	(1.05-1.42)	0.0084
Uncertain	1.14	(0.80-1.62)	0.4498	1.31	(0.89-1.93)	0.1725	1.16	(0.83-1.63)	0.3984
DBP (mmHg)	0.99	(0.98-1.00)	0.0037						
SBP (mmHg)	1.00	(0.99-1.01)	0.2962	0.99	(0.99-0.99)	<0.0001	0.99	(0.99-0.99)	0.0003
eGFR (CKD-EPI formula)(ml/min)				0.99	(0.99-0.99)	<0.0001	0.99	(0.99-0.99)	0.0064
Log-BUN (mmol/L)	1.39	(1.23-1.58)	<0.0001				1.16	(1.02-1.32)	0.0233
Log-NT-proBNP (ng/L)	1.30	(1.18-1.42)	<0.0001	1.12	(1.02-1.23)	0.0205	1.14	(1.05-1.23)	0.0009
Hemoglobin (g/dL)	0.79	(0.68-0.92)	0.0034				0.91	(0.88-0.95)	<0.0001
Hematocrit (g/dL)	1.05	(1.00-1.11)	0.0626						
Sodium (mmol/L)	0.97	(0.95-0.99)	0.0099				0.98	(0.96-1.00)	0.0026
Log-Total Bilirubin (μmol/L)	1.08	(0.92-1,28)	0.3589				1.11	(0.99-1.24)	0.0798
Log-Alkaline Phosphatase (μg/L)	1.38	(1.14-1.67)	0.0011				1.28	(1.09-1.51)	0.0035
HDL (mmol/L)	0.68	(0.51-0.90)	0.0075	0.69	(0.54-0.88)	0.0031	0.72	(0.57-0.90)	0.0042

Use of beta-blocking agent at baseline	0.75	(0.63-0.89)	0.0009	0.74	(0.62-0.88)	0.0007	0.76	(0.67-0.88)	0.0064

Abbreviations: CI: Confidence Interval; eGFR: estimate Glomerular Filtration Rate; HDL: High Density Lipoprotein; NYHA: New York Heart Association class; NT-proBNP: N terminal pro Brain Natriuretic Peptide

Word Count 4830 words (including references, figure legends and tables)

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